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 NEWS  1            Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2            "Ask CAS" for self-help around the clock
 NEWS  3  FEB 25    CA/CAPLUS - Russian Agency for Patents and Trademarks
                    (ROSPATENT) added to list of core patent offices covered
 NEWS  4  FEB 28    PATDPAFULL - New display fields provide for legal status
                    data from INPADOC
 NEWS  5  FEB 28    BABS - Current-awareness alerts (SDIs) available
 NEWS  6  FEB 28    MEDLINE/LMEDLINE reloaded
 NEWS  7  MAR 02    GBFULL: New full-text patent database on STN
 NEWS  8  MAR 03    REGISTRY/ZREGISTRY - Sequence annotations enhanced
 NEWS  9  MAR 03    MEDLINE file segment of TOXCENTER reloaded
 NEWS  10 MAR 22    KOREAPAT now updated monthly; patent information enhanced
 NEWS  11 MAR 22    Original IDE display format returns to REGISTRY/ZREGISTRY
 NEWS  12 MAR 22    PATDPASPC - New patent database available
 NEWS  13 MAR 22    REGISTRY/ZREGISTRY enhanced with experimental property tags
 NEWS  14 APR 04    EPFULL enhanced with additional patent information and new
                    fields
 NEWS  15 APR 04    EMBASE - Database reloaded and enhanced
 NEWS  16 APR 18    New CAS Information Use Policies available online
 NEWS  17 APR 25    Patent searching, including current-awareness alerts (SDIs),
                    based on application date in CA/CAplus and USPATFULL/USPAT2
                    may be affected by a change in filing date for U.S.
                    applications.
 NEWS  18 APR 28    Improved searching of U.S. Patent Classifications for
                    U.S. patent records in CA/CAplus

 NEWS EXPRESS  JANUARY 10 CURRENT WINDOWS VERSION IS V7.01a, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 10 JANUARY 2005

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 NEWS WWW      CAS World Wide Web Site (general information)

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FILE LAST UPDATED: 8 May 2005 (20050508/ED)

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This file contains CAS Registry Numbers for easy and accurate
substance identification.

```
=> s metalloprotease?
L1         4693 METALLOPROTEASE?

=> s psoriasis? () psoriatic () arthritis? IO rheumatoid () arthritis?
          11628 PSORIASIS?
           2757 PSORIATIC
            131 PSORIATICS
           2819 PSORIATIC
                  (PSORIATIC OR PSORIATICS)
          36490 ARTHRITIS?
           3669 IO
            396 IOS
           4061 IO
                  (IO OR IOS)
          25411 RHEUMATOID
             11 RHEUMATOIDS
          25415 RHEUMATOID
                  (RHEUMATOID OR RHEUMATOIDS)
              0 ARTHRITIS? IO RHEUMATOID
                  (ARTHRITIS?(W)IO(W)RHEUMATOID)
          36490 ARTHRITIS?
L2            0 PSORIASIS? (W) PSORIATIC (W) ARTHRITIS? IO RHEUMATOID (W) ARTHRI
                TIS?

=> s psoriasis or arthritis or psoriatic () arthritis or rheumatoid () arthritis?
          11627 PSORIASIS
          36486 ARTHRITIS
              2 ARTHRITISES
          36486 ARTHRITIS
                  (ARTHRITIS OR ARTHRITISES)
           2757 PSORIATIC
            131 PSORIATICS
           2819 PSORIATIC
                  (PSORIATIC OR PSORIATICS)
          36486 ARTHRITIS
              2 ARTHRITISES
          36486 ARTHRITIS
                  (ARTHRITIS OR ARTHRITISES)
            705 PSORIATIC (W) ARTHRITIS
          25411 RHEUMATOID
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           11 RHEUMATOIDS
        25415 RHEUMATOID
                (RHEUMATOID OR RHEUMATOIDS)
        36490 ARTHRITIS?
        22182 RHEUMATOID (W) ARTHRITIS?
L3      44916 PSORIASIS OR ARTHRITIS OR PSORIATIC (W) ARTHRITIS OR RHEUMATOID
              (W) ARTHRITIS?

=> s l3 and l1
L4        289 L3 AND L1

=> s l4 and review/dt
     1820496 REVIEW/DT
L5         38 L4 AND REVIEW/DT

=> s l5 < january 2001
NUMERIC EXPRESSION NOT VALID 'L5 < JANUARY 2001'
Numeric search expressions contain an operator (=,>,<,=<,=>), a field
qualifier, and the number or a range to be searched.  Examples of
valid expressions are 'LD>6', '260-280/MW', and '10 < LD < 30'.  For a
list of field codes in the current file, enter "HELP SFIELDS" at an
arrow prompt (=>).  For more information on searching in numeric
fields, enter "HELP NUMERIC".

=> d l5, ibib abs, 1-38

L5   ANSWER 1 OF 38  HCAPLUS  COPYRIGHT 2005 ACS on STN
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Full Text | Citing References

ACCESSION NUMBER: 2005:146402 HCAPLUS
DOCUMENT NUMBER: 142:328789
TITLE: Recent developments in the design of specific matrix metalloproteinase inhibitors aided by structural and computational studies
AUTHOR(S): Rao, B. Govinda
CORPORATE SOURCE: Vertex Pharmaceuticals Incorporated, Cambridge, MA, 02139, USA
SOURCE: Current Pharmaceutical Design (2005), 11(3), 295-322
CODEN: CPDEFP; ISSN: 1381-6128
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. It was 10 years since a 3-dimensional structure of the catalytic domain of a Matrix **Metalloprotease** (MMP) was revealed for the 1st time in 1994. More than 80 structures of different MMPs in apo and inhibited forms, detd. by x-ray crystallog. and NMR methods, were published by the end of year 2003. A large no. of very potent inhibitors were disclosed in published and patent literature. Several MMP inhibitors entered clin. trials for the treatment of cancer and **arthritis**. Most of the 1st generation inhibitors have hydroxamic acid as the Zinc-binding group and have limited specificity. With the failure of these inhibitors in clin. trials, more efforts were directed to the design of specific inhibitors with different Zn-binding groups in recent years. This review will summarize all the published structural information and focus on the inhibitors that were designed to take advantage of the nonprime side of the MMP active site using structural information and computational anal. Representative structures from all MMPs are aligned to a target structure to provide a better understanding of the similarities and differences of the active site pockets. This anal. supports the view that the differences in the nonprime side pockets provide better opportunities for

designing inhibitors with higher specificity. Published information on all the Zinc-binding groups of MMP inhibitors is reviewed for the 1st time. Pros and cons of inhibitors with non-hydroxamate Zinc-binding groups in terms of specificity, toxicity, and pharmacokinetic properties are discussed.

REFERENCE COUNT: 133 THERE ARE 133 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 38 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2005:32904 HCAPLUS
DOCUMENT NUMBER: 142:233396
TITLE: Neutral endopeptidase and angiotensin-converting enzyme - key enzymes terminating the action of neuroendocrine mediators
AUTHOR(S): Scholzen, Thomas E.; Luger, Thomas A.
CORPORATE SOURCE: Ludwig-Boltzmann Institute of Cell Biology and Immunobiology of the Skin and Department of Dermatology, University of Muenster, Muenster, 48149, Germany
SOURCE: Experimental Dermatology (2004), 13(Suppl. 4), 22-26
CODEN: EXDEEY; ISSN: 0906-6705
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Zinc-**metalloproteases**, such as neutral endopeptidase (NEP) and angiotensin-converting enzyme (ACE), effectively control the bioavailability of peptide mediators released from sensory nerves and immune and skin cells during the cutaneous response to endogenous or exogenous noxious stimuli. Functional inactivation of NEP or ACE by transient inhibition or permanent genomic deletion results in a relative abundance of substance P (SP) and bradykinin (BK); this augments murine allergic contact dermatitis (ACD) by affecting ACD sensitization and elicitation, which involves neurokinin 1 receptors (NK1), BK receptors (B2) and an intact cutaneous sensory nervous system. Present evidence suggests that increased SP via NK1 is capable of boosting important functions of SP- and NK1-expressing dendritic cells (DCs) and T cells (TCs) in an auto- or paracrine manner, which promotes ACID antigen sensitization. Moreover, skin inflammation or wounding in vivo, as well as treatment of epidermal and dermal cells by UV light and inflammatory mediators in vitro, regulates NEP and ACE expression and activity. Likewise, NEP and ACE are capable of processing neuroendocrine hormones, such as ACTH and α-MSH. Thus, present data indicate that ACE and NEP, via proteolytic cleavage of peptide mediators and growth factors, represent important control factors for the inflammatory response in skin disorders such as **psoriasis** or allergic inflammation, but may also be capable of affecting pigmentation, cell survival, wound healing, and tissue regeneration.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 38 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2004:997518 HCAPLUS
DOCUMENT NUMBER: 142:85723
TITLE: Recent advances in the design of matrix **metalloprotease** inhibitors

AUTHOR(S): Matter, Hans; Schudok, Manfred
CORPORATE SOURCE: Aventis Pharma Deutschland GmbH DI and A Chemistry, Frankfurt am Main, D-65926, Germany
SOURCE: Current Opinion in Drug Discovery & Development (2004), 7(4), 513-535
CODEN: CODDFF; ISSN: 1367-6733
PUBLISHER: Thomson Scientific
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Inhibition of matrix **metalloproteases** (MMPs) for the treatment of diseases, such as cancer, **arthritis** and other diseases assocd. with tissue remodeling, has become an area of intense interest in the pharmaceutical industry in recent years. Despite tremendous efforts over the last decade to explore individual members of this target family, along with multiple inhibitor classes, simple and effective drugs for inhibiting individual MMPs have not yet emerged. This review highlights the major developments in research into MMPs and their inhibitors, from the recent medicinal chem. literature, with a focus on structure-based design, selectivity and pharmacokinetic (PK) properties. The increasing availability of high-resoln. x-ray crystal structures for many members of this protein family makes MMPs ideally suited for structure-based design approaches, which are now routinely used in this area. The most challenging aspect of lead optimization for MMP inhibitors is in finding candidates having acceptable pharmacol., PK and selectivity profiles. Clin. trials in cancer giving disappointing results have led to discussions on how to gain adequate MMP selectivity to minimize side effects. Unfortunately, careful anal. of x-ray crystal structures has not suggested any simple solns. These areas collectively constitute the main challenges in the current search for orally available MMP inhibitors, and will be discussed in this review.

REFERENCE COUNT: 133 THERE ARE 133 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 38 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2004:720840 HCAPLUS
DOCUMENT NUMBER: 142:85604
TITLE: **Metalloprotease** inhibitors as anti-inflammatory agents: An evolving target?
AUTHOR(S): Whelan, Clifford J.
CORPORATE SOURCE: Phlogopharm Ltd, Herts, SG9 9JQ, UK
SOURCE: Current Opinion in Investigational Drugs (Thomson Scientific) (2004), 5(5), 511-516
CODEN: COIDAZ; ISSN: 1472-4472
PUBLISHER: Thomson Scientific
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. The **metalloproteases** (MMPs) are a family of enzymes that are important for tissue remodeling. These enzymes have been implicated in a no. of pathologies, including cancer, **arthritis**, atherosclerosis and chronic obstructive pulmonary disease. Thus, inhibitors of MMPs may have utility in the therapy of inflammatory diseases, particularly in **arthritis** where current therapies do not halt the progression of the disease. Many compds. have been identified as inhibitors of MMPs, and some have progressed to the clinic. However, no compd. developed as an MMP inhibitor has been licensed for clin. use thus far. This review discusses this therapeutic area and compares inhibitors of MMPs with other novel therapeutic approaches in the treatment of inflammatory disease.

Inhibitors of MMPs may find utility in disorders not currently targeted, but where MMPs are involved in the pathol.
REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 38 HCAPLUS COPYRIGHT 2005 ACS on STN
Full Text | Citing References
ACCESSION NUMBER: 2004:676240 HCAPLUS
DOCUMENT NUMBER: 142:197614
TITLE: The design and synthesis of aryl hydroxamic acid inhibitors of MMPs and TACE
AUTHOR(S): Levin, Jeremy I.
CORPORATE SOURCE: Wyeth Research, Pearl River, NY, 10965, USA
SOURCE: Current Topics in Medicinal Chemistry (Sharjah, United Arab Emirates) (2004), 4(12), 1289-1310
CODEN: CTMCCL; ISSN: 1568-0266
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review. Three different classes of aryl hydroxamic acid scaffolds have been explored and provided potent inhibitors of MMP-1, -2, -9, -13 and TACE. Structure-based design has allowed the evolution of these inhibitors from broad spectrum inhibitors into compds. that are more selective for MMPs relevant to particular disease states. Aryl hydroxamates selective for MMP-9, MMP-13 and TACE have been disclosed that may aid in the study of the physiol. role of these enzymes. Furthermore, the different selectivity profiles offered by these MMP/TACE inhibitors may allow the detn. of which **metalloprotease**, or group of **metalloproteases**, must be inhibited for the safe, long-term treatment of osteoarthritis, **rheumatoid arthritis** and cancer. Some of these compds. have demonstrated useful biol. activity in efficacy models relevant to osteoarthritis and **rheumatoid arthritis** and are therefore potential clin. candidates.
REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 6 OF 38 HCAPLUS COPYRIGHT 2005 ACS on STN
Full Text | Citing References
ACCESSION NUMBER: 2004:455774 HCAPLUS
DOCUMENT NUMBER: 141:388002
TITLE: Targeted proteomics: activity-based enrichment of matrix **metalloproteases**
AUTHOR(S): Freije, J. R.; Klein, T.; Bischoff, R.
CORPORATE SOURCE: Center for Pharmacy, University of Groningen, Groningen, 9713 AV, Neth.
SOURCE: BIOforum Europe (2004), 8(2), 55-57
CODEN: BEIUB6; ISSN: 1611-597X
PUBLISHER: GIT Verlag GmbH & Co. KG
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review. Chronic inflammatory disease is often assocd. with an excess of uncontrolled proteolytic activity. This leads to tissue destruction and irreversible damage as seen, for example, in the development of pulmonary emphysema during Chronic Obstructive Pulmonary Disease (COPD) or joint destruction in **Rheumatoid Arthritis**. Migration of cells requires also proteolytic activity often assocd. with the cellular membrane to traverse the extracellular matrix. Metastatic cancer cells thus require such activities to evade from their primary location and to invade distant

sites in the body. Matrix **Metalloproteases** (MMPs) are one important class of enzymes that can essentially degrade all of the constituents of the extracellular matrix and have attracted considerable attention as drug targets. Despite these efforts little is known about their activity under disease-relevant conditions due to a lack of suitable methods. This has lead to a situation, where the effect of many new drug candidates cannot be assessed directly at the mechanistic, biochem. level. In the following we will describe a novel approach to profile MMPs in an activity-dependent way by targeted proteomics based on reversible active-site directed protease inhibitors.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 7 OF 38 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2004:322446 HCAPLUS
DOCUMENT NUMBER: 141:407589
TITLE: A disintegrin-like and **metalloprotease** (reprolysin type) with thrombospondin type 1 motifs: the ADAMTS family
AUTHOR(S): Apte, Suneel S.
CORPORATE SOURCE: Lerner Research Institute, Department of Biomedical Engineering, (ND20), Cleveland Clinic Foundation, Cleveland, OH, 44195, USA
SOURCE: International Journal of Biochemistry & Cell Biology (2004), 36(6), 981-985
CODEN: IJBBFU; ISSN: 1357-2725
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. ADAMTS proteases are complex secreted enzymes contg. a prometalloprotease domain of the reprolysin type attached to an ancillary domain with a highly conserved structure that includes at least one thrombospondin type 1 repeat. Known functions of ADAMTS proteases include processing of procollagens and von Willebrand factor as well as catabolism of aggrecan, versican and brevican. They have been demonstrated to have important roles in connective tissue organization, coagulation, inflammation, **arthritis**, angiogenesis and cell migration. ADAMTS can be grouped into distinct clades within which there is conservation of modular organization, protein sequence, gene structure and possibly, of substrate preference. ADAMTS proteases are synthesized as zymogens, with constitutive proprotein convertase removal of the propeptide occurring prior to secretion. Their enzymic specificity is heavily influenced by their ancillary domain, which plays a crit. role in directing these enzymes to their substrates, the cell surface and the extracellular matrix.

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 8 OF 38 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2004:245840 HCAPLUS
DOCUMENT NUMBER: 141:46590
TITLE: Matrix **metalloprotease** inhibitors: design from structure
AUTHOR(S): Borkakoti, N.
CORPORATE SOURCE: Chemical Technologies, Roche Products Ltd, Welwyn Garden City, AL7 3AY, UK

SOURCE: Biochemical Society Transactions (2004), 32(1), 17-20
CODEN: BCSTB5; ISSN: 0300-5127
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review and discussion. The Zn2+- and Ca2+-dependent family of proteins called matrix **metalloproteases** (MMPs) are collectively responsible for the degrdn. of the extracellular matrix. The enzymes are synthesized as zymogens, and under physiol. conditions are selectively regulated by endogenous inhibitors. An imbalance between the active enzymes and their natural inhibitors leads to the accelerated destruction of connective tissue assocd. with the pathol. of diseases such as **arthritis**, cancer, multiple sclerosis, and cardiovascular diseases. The potential for using specific enzyme inhibitors, such as Trocade, as therapeutic agents to redress this balance has led to intensive research focused on the design, synthesis and mol. deciphering of low-mol.-wt. inhibitors of this family of proteins. The design of early MMP inhibitors was based on the scissile site sequence of peptide substrates, with moieties customized to chelate the crit. Zn2+ ion at the enzyme active site. These initial efforts have been supported by x-ray and NMR data on MMP complexes, exploiting sequence and structural differences in the principal specificity pocket of the enzymes, leading to subtype-selective MMP inhibitors. This review provides a crit. appraisal of the design principles that have been utilized in generating mols. that inhibit MMPs, and explores issues relevant to obtaining clin. efficacy of MMP inhibitor-based therapies.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 9 OF 38 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2003:824397 HCAPLUS
DOCUMENT NUMBER: 140:251855
TITLE: An outline of laboratory tests for autoimmune disorders
AUTHOR(S): Misaki, Yoshikata
CORPORATE SOURCE: Department of Allergy & Rheumatology, Tokyo University Hospital, Japan
SOURCE: Rinsho Byori Rebyu, Tokushugo (2003), 124, 57-65
CODEN: RBRTF3
PUBLISHER: Rinsho Byori Kankokai
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: Japanese

AB A review. The topics discussed are (1) general clin. tests for **arthritis**; (2) immunol. tests for detecting autoantibodies including rheumatic factor (RF), antinuclear antibody, anti-phospholipid antibody, lupus anticoagulant (LA), and anti-neutrophil cytoplasmic antibody (ANCA); (3) detection of complements and immune complexes in innate immunity; (4) detection of Igs, cryoglobulins and serum amyloid A (SAA); (5) matrix **metalloprotease** 3 (MMP-3) in evaluation of cartilage destruction; (6) creatine in evaluation of muscle abnormality; (7) KL-6 and surfactant protein D (SP-D) in evaluation of interstitial lung inflammation; (8) bone formation and resorption markers for osteoporosis; and (9) microbial antigens for infectious disease.

L5 ANSWER 10 OF 38 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2003:817436 HCAPLUS
DOCUMENT NUMBER: 140:156465

TITLE: Design strategies for the identification of MMP-13 and TACE inhibitors
AUTHOR(S): Skotnicki, Jerauld S.; DiGrandi, Martin J.; Levin, Jeremy I.
CORPORATE SOURCE: Chemical and Screening Sciences, Wyeth Research, New York, NY, 10965, USA
SOURCE: Current Opinion in Drug Discovery & Development (2003), 6(5), 742-759
CODEN: CODDFF; ISSN: 1367-6733
PUBLISHER: Current Drugs
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review. Inhibitors of matrix **metalloprotease** (MMP)-13 and tumor necrosis factor-α converting enzyme (TACE) have been highly sought as potential therapeutic agents for the treatment of osteoarthritis and **rheumatoid arthritis**, resp. This review focuses on the published literature on these inhibitors from 2001 to mid-2003. Significant advances have been reported in the design and synthesis of potent and selective inhibitors of MMP-13 using hydroxamic acid and non-hydroxamate zinc chelators on a variety of scaffolds. TACE inhibitors based on variations of known MMP inhibitor scaffolds and novel designs have been reported. Selectivity profiles for these inhibitors range from broad-spectrum to TACE-specific. Future clin. studies on these and other inhibitors will det. which MMP, or set of MMPs, must be inhibited for efficacy and long-term safety.
REFERENCE COUNT: 94 THERE ARE 94 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 11 OF 38 HCAPLUS COPYRIGHT 2005 ACS on STN
Full Text | Citing References
ACCESSION NUMBER: 2003:754330 HCAPLUS
DOCUMENT NUMBER: 140:121868
TITLE: Protease inhibitors of the sulfonamide type: anticancer, antiinflammatory, and antiviral agents
AUTHOR(S): Supuran, Claudiu T.; Casini, Angela; Scozzafava, Andrea
CORPORATE SOURCE: Dipartimento di Chimica, Laboratorio di Chimica Bioinorganica, Universita degli Studi di Firenze, Sesto Florentino, I-50019, Italy
SOURCE: Medicinal Research Reviews (2003), 23(5), 535-558
CODEN: MRREDD; ISSN: 0198-6325
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review. The sulfonamides constitute an important class of drugs, with several types of pharmacol. agents possessing antibacterial, anticarbonic anhydrase, diuretic, hypoglycemic, and antithyroid activity among others. A large no. of structurally novel sulfonamide derivs. have ultimately been reported to show substantial protease inhibitory properties. Of particular interest are some **metalloprotease** inhibitors belonging to this class, which by inhibiting several matrix **metalloproteases** (MMPs) show interesting antitumor properties. Some of these compds. are currently being evaluated in clin. trials. The large no. of sulfonamide MMP inhibitors ultimately reported also lead to the design of effective tumor necrosis factor-α converting enzyme (TACE) inhibitors, potentially useful in the treatment of inflammatory states of various types. Since both MMPs and TACE contribute synergistically to the pathophysiol. of many diseases, such as **arthritis**, bacterial meningitis, tumor invasion; the dual inhibition of these enzymes emerged as an

interesting target for the drug design of anticancer/antiinflammatory drugs, and many such sulfonamide derivs. were recently reported. Human neutrophil elastase (HNE) inhibitors of the sulfonamide type may also be useful in the treatment of inflammatory conditions, such as emphysema, cystic fibrosis, chronic bronchitis, ischemia reperfusion injury, and acute respiratory distress syndrome. Inhibition of some cysteine proteases, such as several caspase and cathepsin isoenzymes, may lead to the development of pharmacol. agents effective for the management of several diseases, such as **rheumatoid arthritis**, inflammatory bowel disease, brain damage, and stroke. Another research line that progressed much in the last time regards different sulfonamides with remarkable antiviral activity. Some clin. used HIV protease inhibitors (such as amprenavir) possess sulfonamide moieties in their mols., which are crit. for the potency of these drugs, as shown by x-ray crystallog., whereas a very large no. of other derivs. are constantly being synthesized and evaluated to obtain compds. with lower toxicity or augmented activity against viruses resistant to the such first generation drugs. Other viral proteases, such as those isolated from several types of herpes viruses may be inhibited by sulfonamide derivs., leading thus to more effective classes of antiviral drugs.

REFERENCE COUNT: 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 12 OF 38 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2003:339429 HCAPLUS
DOCUMENT NUMBER: 139:50739
TITLE: The ADAMs family of proteins: From basic studies to potential clinical applications
AUTHOR(S): Duffy, Michael J.; Lynn, David J.; Lloyd, Andrew T.; O'Shea, Caroline M.
CORPORATE SOURCE: Department of Nuclear Medicine, St Vincent's University Hospital, Dublin, 4, Ire.
SOURCE: Thrombosis and Haemostasis (2003), 89(4), 622-631
CODEN: THHADQ; ISSN: 0340-6245
PUBLISHER: Schattauer GmbH
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. The ADAMs are a family of membrane proteins possessing a disintegrin and **metalloprotease** domain. Currently, 34 members are known to exist. Approx. 50% of the ADAMs contain a **metalloprotease**-like domain and some of these have been shown to possess protease activity. Most of the protein substrates identified to date for ADAMs are either integral membrane or extracellular matrix (ECM) proteins. In addn. to hydrolyzing proteins, a no. of ADAMs bind to integrins. The attachment to integrins occurs via the disintegrin domain. Since the ADAMs can play a role in both proteolysis and adhesion, they were implicated in a variety of biol. processes such as sperm-egg fusion, somatic cell-cell adhesion, ectodomain shedding, myoblast fusion and development. Altered expression of certain ADAMs has been assocd. with a no. of diseases including asthma, **arthritis**, Alzheimer's disease, atherosclerosis and cancer.

REFERENCE COUNT: 107 THERE ARE 107 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 13 OF 38 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2003:297317 HCAPLUS

DOCUMENT NUMBER: 140:108913
TITLE: MMPs: They are there and they do something - also in Dermatology
AUTHOR(S): Egelrud, Torbjoern
CORPORATE SOURCE: Swed.
SOURCE: Acta Dermato-Venereologica (2003), 83(2), 81-82
CODEN: ADVEA4; ISSN: 0001-5555
PUBLISHER: Taylor & Francis
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review discusses recent findings demonstrating the potential importance and complexity of a well regulated matrix **metalloprotease** (MMP) activity and expression in the skin. A study by Suomela et al. (ibid., 108) evaluates the expression of structurally related enzymes MMP-19 and MMP-28 in **psoriasis** and lichen planus. MMP-19 was expressed by psoriatic lesional keratinocytes in vivo as well as in vitro, but not by non-lesional psoriatic or normal keratinocytes, while MMP-28 was not expressed by keratinocytes in **psoriasis** or lichen planus. Suomela et al. suggested that total destruction of the basement membrane, like in wounds, could be needed to induce expression of MMP-28 by proliferating keratinocytes. An in vitro study by Kobayashi et al. (ibid., 105) shows that cultured fibroblasts secreted only MMP-2 in the absence of added cytokines or growth factors, while unstimulated cultured keratinocytes secreted both MMP-2 and MMP-9.

L5 ANSWER 14 OF 38 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2003:142819 HCAPLUS
DOCUMENT NUMBER: 139:4337
TITLE: Can one estimate the progression of joint destruction using joint markers
AUTHOR(S): Yamada, Harumoto
CORPORATE SOURCE: Dep. Orthop. Surg., Fujita Health Univ., Japan
SOURCE: Gendai Igaku (2002), 50(2), 203-209
CODEN: GEIGAI; ISSN: 0433-3047
PUBLISHER: Aichi-ken Ishikai
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: Japanese
AB A review on joint biomarkers for diagnosis of bone destruction in osteoarthritis (OA) and **rheumatoid arthritis** (RA). Pathol. and mechanism of joint destruction and known biomarkers of joints are discussed here. Joint biomarkers are classified into cartilage and joint inflammatory markers which include keratin sulfate, epitope 846, epitope 3-B-(-), matrix **metalloprotease** (MMP) and C-terminal type II procollagen peptide.

L5 ANSWER 15 OF 38 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2003:115030 HCAPLUS
DOCUMENT NUMBER: 138:301363
TITLE: **Metalloproteases** and inhibitors in arthritic diseases
AUTHOR(S): Martel-Pelletier, Johanne; Welsch, Dean J.; Pelletier, Jean-Pierre
CORPORATE SOURCE: Osteoarthritis Research Unit, Hopital Notre-Dame, Centre Hospitalier de l'Universite de Montreal, Montreal, QC, Can.
SOURCE: Best Practice & Research, Clinical Rheumatology (2001), 15(5), 805-829

CODEN: BPRCC7
PUBLISHER: Bailliere Tindall
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review. Controlling degrdn. of the extracellular matrix is crucial in arthritic diseases such as osteoarthritis (OA) and **rheumatoid arthritis** (RA), as conventional treatments do not pos. affect the structural properties of the articular tissues. **Metalloproteases**, a family of zinc-dependent enzymes, and more specifically the matrix **metalloproteases** (MMPs), play a premier role in joint articular tissue degeneration. Addnl. enzymes of the **metalloprotease** family, such as the membrane-type **metalloproteases** (MT-MMPs) and the adamalysins that include the ADAMs and the ADAMTS families, have also been involved in these disease processes. At present, therapeutic intervention based on the inhibition of **metalloproteases**, and more particularly of the MMPs, is under intensive investigation, and several MMP inhibitors are in clin. development. Currently, MMP inhibitors are exemplified by several chem. classes: hydroxamic acids, carboxylic acids and thiols. One key issue in the clin. development of MMP inhibitors relates to whether broad-spectrum inhibitors active against a range of different enzymes or selective inhibitors targeted against a single enzyme or particular subset of the MMPs represents the optimal strategy. In this chapter, the authors address the different **metalloprotease** enzymes and sub-families and their implication in arthritic diseases. Furthermore, the authors assess physiol. and chem. **metalloprotease** inhibitors, and for the latter, the current inhibitory classes of compds. being studied.
REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 16 OF 38 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:842640 HCAPLUS
DOCUMENT NUMBER: 138:296924
TITLE: Sulfonamide derivatives with protease inhibitory action as anticancer, anti-inflammatory and antiviral agents
AUTHOR(S): Casini, Angela; Scozzafava, Andrea; Supuran, Claudiu T.
CORPORATE SOURCE: Dipartimento di Chimica, Laboratorio di Chimica Bioinorganica, Universita degli Studi di Firenze, Sesto Fiorentino, Florence, I-50019, Italy
SOURCE: Expert Opinion on Therapeutic Patents (2002), 12(9), 1307-1327
CODEN: EOTPEG; ISSN: 1354-3776
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review. A large no. of sulfonamide derivs. have ultimately been reported to show substantial protease inhibitory properties. Some matrix **metalloprotease** (MMP) inhibitors belonging to this class show significant antitumor properties. Such compds. also lead to the design of effective tumor TNF-α converting enzyme (TACE) inhibitors, potentially useful in the treatment of inflammatory states. Since both MMPs and TACE contribute synergistically to the pathophysiol. of many diseases (**arthritis**, bacterial meningitis, tumor invasion etc.), the dual inhibition of these enzymes emerged as an interesting target for the drug design of anticancer/anti-inflammatory drugs. Human neutrophil elastase (HNE) inhibitors of the sulfonamide type may also be useful in the treatment of inflammatory conditions such as emphysema, cystic

fibrosis, chronic bronchitis, ischemia - reperfusion injury and acute respiratory distress syndrome. Inhibition of cysteine proteases, such as several caspase and cathepsin isoenzymes, may lead to the development of pharmacol. agents effective for the management of **rheumatoid arthritis**, inflammatory bowel disease, brain damage and stroke. Another research line that has progressed recently regards different sulfonamides with remarkable antiviral activity. Some clin. used HIV protease inhibitors, such as amprenavir (Agenerase, Vertex Pharmaceuticals, Inc.), possess sulfonamide moieties in their mols., whereas a very large no. of other derivs. are constantly being synthesized and evaluated to obtain compds. with lower toxicity or augmented activity against viruses resistant to the first generation of such drugs.

REFERENCE COUNT: 119 THERE ARE 119 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 17 OF 38 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Cited References

ACCESSION NUMBER: 2002:639168 HCAPLUS
DOCUMENT NUMBER: 138:180050
TITLE: Hydroxamic acids as pharmacological agents
AUTHOR(S): Muri, E. M. F.; Nieto, M. J.; Sindelar, R. D.; Williamson, J. S.
CORPORATE SOURCE: Department of Medicinal Chemistry, School of Pharmacy, University of Mississippi, University, MS, 38677, USA
SOURCE: Current Medicinal Chemistry (2002), 9(17), 1631-1653
CODEN: CMCHE7; ISSN: 0929-8673
PUBLISHER: Bentham Science Publishers
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. A variety of hydroxamic acid derivs. have recently been touted for their potential use as inhibitors of hypertension, tumor growth, inflammation, infectious agents, asthma, **arthritis**, and more. Here we provide a comprehensive review of the basic medicinal chem. and pharmacol. of hydroxamic acid derivs. that have been examd. as inhibitors of zinc **metalloproteases**, matrix metalloproteinases, leukotriene A4 hydrolases, ureases, lipoxygenases, cyclooxygenases, as well as peptide deformilases.

REFERENCE COUNT: 157 THERE ARE 157 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 18 OF 38 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Cited References

ACCESSION NUMBER: 2002:199289 HCAPLUS
DOCUMENT NUMBER: 136:338400
TITLE: Functional and biochemical characterization of ADAMs and their predicted role in protein ectodomain shedding
AUTHOR(S): Blobel, C. P.
CORPORATE SOURCE: Cellular Biochemistry and Biophysics Program, Memorial Sloan-Kettering Cancer Center, Sloan-Kettering Institute, New York, NY, 10021, USA
SOURCE: Inflammation Research (2002), 51(2), 83-84
CODEN: INREFB; ISSN: 1023-3830
PUBLISHER: Birkhaeuser Verlag
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with emphasis on researcher's study. Proteolysis on the cell

surface and in the extracellular matrix is essential for normal cellular functions during development and in the adult, but it may also have undesirable consequences by promoting diseases such as cancer, **arthritis**, and Alzheimer's disease. A particularly interesting function of proteolysis on the cell surface is to release ectodomains of membrane proteins from the plasma membrane. This process, which is referred to as protein ectodomain shedding, affects a variety of proteins with important roles in development and in disease, including cytokines, growth factors, receptors, adhesion proteins and other proteins such as the amyloid precursor protein. In principle, protein ectodomain shedding can dramatically change the properties of a substrate protein. For example, membrane anchored growth factors such as transforming growth factor-α (TGF-α) are only able to activate their receptor, the epidermal growth factor receptor (EGFR), after they are shed from the plasma membrane. Inhibitor studies have implicated zinc-dependent **metalloproteases** in protein ectodomain shedding, and in particular a family of **metalloproteases** termed ADAMs (a disintegrin and **metalloprotease**). The main focus of my lab. is to understand the role of different ADAMs in protein ectodomain shedding, and to learn about the functional consequences of protein ectodomain shedding for individual substrates.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 19 OF 38 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:34339 HCAPLUS
DOCUMENT NUMBER: 137:31037
TITLE: Articular cartilage and changes in **arthritis**: matrix degradation
AUTHOR(S): Mort, John S.; Billington, Caron J.
CORPORATE SOURCE: Joint Diseases Laboratory, Shriners Hospital for Children, Montreal, QC, Can.
SOURCE: Arthritis Research [online computer file] (2001), 3(6), 337-341
CODEN: ARESFU; ISSN: 1465-9913
URL: http://arthritis-research.com/content/pdf/AR-3-6-337.pdf
PUBLISHER: BioMed Central Ltd.
DOCUMENT TYPE: Journal; **General Review**; (online computer file)
LANGUAGE: English

AB A review. While many proteases in articular cartilage have been described, current studies indicate that members of two families of **metalloproteases** - MMPs and the ADAMTSs - are responsible for the degrdn. of the major components of this tissue. Collagenases (MMPs) make the first cleavage in triple-helical collagen, allowing its further degrdn. by other proteases. Aggrecanases (ADAMTSs), in conjunction with other MMPs, degrade aggrecan, a component of the proteoglycan aggregate. Anti-neoepitope antibodies that recognize the cleavage products of collagen and aggrecan generated by these enzymes are now available and are being used to detect the sites of action and to quantitate degrdn. products.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 20 OF 38 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:259436 HCAPLUS

DOCUMENT NUMBER: 136:272422
TITLE: TACE and other ADAM proteases as targets for drug discovery
AUTHOR(S): Moss, M. L.; White, J. M.; Lambert, M. H.; Andrews, R. C.
CORPORATE SOURCE: Cognosci, Research Triangle Park, NC, 27709, USA
SOURCE: Drug Discovery Today (2001), 6(8), 417-426
CODEN: DDTOFS; ISSN: 1359-6446
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Tumor necrosis factor (TNF)-converting enzyme (TACE) and other ADAM proteases (those that contain a disintegrin and a **metalloprotease** domain) have emerged as potential therapeutic targets in the areas of **arthritis**, cancer, diabetes and HIV cachexia. TACE is the first ADAM protease to process the known physiol. substrate and inflammatory cytokine, membrane-bound precursor-TNF-α, to its mature sol. form. Subsequently, TACE was shown to be required for several different processing events such as tumor growth factor-α (TGF-α) precursor and amyloid precursor protein (APP) cleavage. With the recent discoveries of the proteolytic specificities of other ADAM family members, the information surrounding these **metalloproteases** is expanding at an exponential rate. This review focuses on TACE and other family members with known proteolytic function as well as the inhibitors of this class of enzyme.

REFERENCE COUNT: 104 THERE ARE 104 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 21 OF 38 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | More References

ACCESSION NUMBER: 2001:97803 HCAPLUS
DOCUMENT NUMBER: 134:291847
TITLE: ADAMTS: a novel family of extracellular matrix proteases
AUTHOR(S): Tang, B. L.
CORPORATE SOURCE: Central Imaging and Histology Facility, Institute of Molecular and Cell Biology, Singapore, 117609, Singapore
SOURCE: International Journal of Biochemistry & Cell Biology (2001), 33(1), 33-44
CODEN: IJBBFU; ISSN: 1357-2725
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with 61 refs. ADAMTS (a disintegrin and **metalloprotease** with thrombospondin motifs) is a novel family of extracellular proteases found in both mammals and invertebrates. Members of the family may be distinguished from the ADAM (a disintegrin and **metalloprotease**) family members based on the multiple copies of thrombospondin 1-like repeats they carry. With at least nine members in mammals alone, the ADAMTS family members are predicted by their structural domains to be extracellular matrix (ECM) proteins with a wide range of activities and functions distinct from members of the ADAM family that are largely anchored on the cell surface. ADAMTS2 is a procollagen N-proteinase, and the mutations of its gene are responsible for Human Ehlers-Danlos syndrome type VII C and bovine dermatosparaxis. ADAMTS4 and ADAMTS5 are aggrecanases implicated in the degrdn. of cartilage aggrecan in arthritic diseases. Other members of the ADAMTS family have also been implicated in roles during embryonic

development and angiogenesis. Current and future studies on this emerging group of ECM proteases may provide important insights into developmental or pathol. processes involving ECM remodeling.
REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 22 OF 38 HCAPLUS COPYRIGHT 2005 ACS on STN
Full Text | Citing References

ACCESSION NUMBER: 2000:614230 HCAPLUS
DOCUMENT NUMBER: 133:290556
TITLE: Ajulemic acid (CT3): a potent analog of the acid metabolites of THC
AUTHOR(S): Burstein, Sumner H.
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, University of Massachusetts Medical School, Worcester, MA, 01655, USA
SOURCE: Current Pharmaceutical Design (2000), 6(13), 1339-1345
CODEN: CPDEFP; ISSN: 1381-6128
PUBLISHER: Bentham Science Publishers
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with 19 refs. The acid metabolites of THC were discovered almost 30 yr ago and were later shown to posses modest analgesic and anti-inflammatory activity in a variety of models. Ajulemic acid (CT3) is a more potent analog of THC-11-oic acid in which a dimethylheptyl side chain is substituted for the pentyl side chain of the naturally occurring metabolite. It produces analgesia in the mouse hot plate, the PPQ writhing, the formalin and the tail clip assays. In the latter, it was equipotent to morphine; however, it showed a much greater duration of action. In the paw edema, s.c. air pouch and rat adjuvant-induced **arthritis** models of inflammation; it showed significant therapeutic activity at a dose of 0.2 mg/kg p.o. In the **arthritis** model it greatly reduced permanent damage to joints when compared to an indomethacin control as evidenced by an improved joint score over vehicle controls and by histopathol. examn. In contrast to the NSAIDs, it was totally nonulcerogenic at therapeutically relevant doses. Moreover, it does not depress respiration, exhibit dependence, induce body wt. loss or cause mutagenesis. It shows none of the typical actions in models of the psychotropic actions of cannabinoids suggesting that a good sepn. of desirable from undesirable effects was achieved. Studies on its mechanism of action are currently underway. The data thus far suggest the existence of a novel receptor for ajulemic acid with possible downstream effects on eicosanoid prodn., cytokine synthesis and **metalloprotease** activity. There is also circumstantial evidence for a putative endogenous ajulemic acid, namely, arachidonylglycine.
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 23 OF 38 HCAPLUS COPYRIGHT 2005 ACS on STN
Full Text | Citing References

ACCESSION NUMBER: 2000:165673 HCAPLUS
DOCUMENT NUMBER: 132:178736
TITLE: What is new in orthopedic pathology?
AUTHOR(S): Roessner, A.; Eberhardt, R.; Hackel, C.; Pap, G.; Walter, H.; Nebelung, W.; Neumann, H. W.
CORPORATE SOURCE: Institut fur Pathologie, Otto-von-Guericke Universitat Magdeburg, Germany
SOURCE: Verhandlungen der Deutschen Gesellschaft fuer

Pathologie (1999), 83(Pathologie des Gastrointestinaltraktes), 184-194
CODEN: VDGPAN; ISSN: 0070-4113
PUBLISHER: Urban & Fischer Verlag
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: German

AB A review is given with 29 refs. including the author's own works. The term orthopedic pathol. refers to bone- and joint-affecting diseases which are important for the orthopedic surgeon. In the report presented here, emphasis is placed on the membrane-assocd. proteolysis, which is essential for the degrdn. of the extracellular matrix. Matrix-degrading processes play a role not only in arthrosis but also in **rheumatoid arthritis**. Moreover, they are strongly assocd. with the problem of loosening of protheses, which is of utmost importance for the orthopedic surgeon. In these processes, major roles are played by the plasminogen activator system, plasmin, different matrix metalloproteinases, including the membrane type matrix **metalloproteases** and different cathepsins. A deeper insight into the function of these proteins and their influence on the matrix degrdn. in joint diseases will open the way for new diagnostic and therapeutic strategies. Investigations into a large no. of chondrosarcomas have shown that for this type of bone lesions, urokinase plasminogen activator and cathepsin B are prognostic parameters that are independent of the differentiation grade. Also, in this context, investigations into the membrane-bound proteases will be of great practical and diagnostic value.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 24 OF 38 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2000:124506 HCAPLUS
DOCUMENT NUMBER: 133:37574
TITLE: The role of **metalloprotease** inhibitors in cancer and chronic inflammatory diseases
AUTHOR(S): Rasmussen, H. S.; Lynch, K. P.
CORPORATE SOURCE: Clinical Research and Regulatory Affairs, British Biotech, Inc., Annapolis, MD, 21405, USA
SOURCE: Handbook of Experimental Pharmacology (2000), 140(Proteases as Targets for Therapy), 221-234
CODEN: HEPHD2; ISSN: 0171-2004
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with many refs. There is a growing body of evidence confirming that excessive prodn. of **metalloproteases** (MMPs) plays an important role in the growth and spread of malignant tumors, including colorectal, lung, breast, cervical and prostate cancers. Inhibitors of these enzymes have proven effective in a range of preclin. cancer models (ovarian, colorectal, brain, lung, pancreas, gastric, melanoma), slowing the growth of the tumor as well as reducing the incidence of metastases. Some data suggest that the optimal setting for drugs of this nature is in earlier-stage disease or tumors of low vol., and that longer-term treatment has advantages over short-term therapy. It is nevertheless clear that these agents represent a promising possibility for an addnl. weapon in the treatment of cancer. Phase-I/II studies in patients with advanced cancers have demonstrated that the drugs are generally well tolerated without the toxicity which characterizes traditional cytotoxic agents. Randomized clin. trials are now underway to establish their potential efficacy. Theor., MMP inhibitors (MMPIs) may also be useful in

the treatment of **arthritis**, inflammatory bowel disease, periodontal disease, graft-vs.-host reaction and some cardiol. diseases; however, the research of these indications remains predominantly at the preclin. stage.
REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 25 OF 38 HCAPLUS COPYRIGHT 2005 ACS on STN
Full Text | Citing References
ACCESSION NUMBER: 1999:419273 HCAPLUS
DOCUMENT NUMBER: 131:42768
TITLE: Destruction of rheumatoid articular cartilage by proteinases
AUTHOR(S): Okada, Yasunori
CORPORATE SOURCE: Sch. Med., Keio Univ., Japan
SOURCE: Byori to Rinsho (1999), 17(7), 711-717
CODEN: BYRIEM; ISSN: 0287-3745
PUBLISHER: Bunkodo
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: Japanese
AB A review with 28 refs., on characteristics of ECM (extracellular matrix)-degrading proteases, esp. matrix metalloproteinase (MMP), expression of MMP in rheumatoid articular (RA) tissues, MMP activity regulatory mechanism, and involvement of ADAM (a disintegrin and **metalloprotease** domain) gene family in destruction of rheumatoid articular cartilage.

L5 ANSWER 26 OF 38 HCAPLUS COPYRIGHT 2005 ACS on STN
Full Text | Citing References
ACCESSION NUMBER: 1999:305305 HCAPLUS
DOCUMENT NUMBER: 131:124784
TITLE: Cysteine proteases as therapeutic targets
AUTHOR(S): Bromme, Dieter
CORPORATE SOURCE: Dept. of Human Genetics, Mount Sinai School of Medicine, New York, NY, 10029, USA
SOURCE: Drug News & Perspectives (1999), 12(2), 73-82
CODEN: DNPEED; ISSN: 0214-0934
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with 93 refs. Protease-targeted drugs are not common, although **metalloprotease** inhibitors have been favored in recent years. Cysteine proteases of the papain superfamily have been viewed as less attractive drug targets until recently, due to the former view that they were unspecific and ubiquitously distributed. However, many novel findings on papain-like cysteine proteases have been made. Presently there are at least 12 human proteases of the papain family from which sequences have been obtained (cathepsins B, L, H, S, O, K, C, W, F, V(L2), Z(X) and bleomycin hydrolase). Several of these new enzymes have a restricted tissue distribution, which implies specific cellular functions, and thus would allow a specific targeting of these activities without interfering with the general lysosomal protein degrdn. The cathepsins have been found to participate in a no. of diseases such as osteoporosis, **rheumatoid arthritis**, osteoarthritis and cancer, as well as in immune response and neurodegeneration.
REFERENCE COUNT: 93 THERE ARE 93 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 27 OF 38 HCAPLUS COPYRIGHT 2005 ACS on STN

Full-Text | Citing References

ACCESSION NUMBER: 1999:280989 HCAPLUS
DOCUMENT NUMBER: 131:16699
TITLE: Membrane type-**metalloprotease** and bone and cartilage destruction
AUTHOR(S): Takizawa, Masayuki; Okada, Yasunori
CORPORATE SOURCE: Sch. Med., Keio Univ., Japan
SOURCE: Ensho to Men'eki (1999), 7(3), 263-270
CODEN: ENMEFA; ISSN: 0918-8371
PUBLISHER: Sentan Igakusha
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: Japanese
AB A review with 29 refs. on structures, functions, and expressions in cartilages with **rheumatoid arthritis** and osteoarthritis of MT-MMP (membrane-type-matrix metalloproteinases) and ADAM (proteins with a disintegrin and metalloproteinase domain) family and on involvement of MMP in bone resorption.

L5 ANSWER 28 OF 38 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1999:233233 HCAPLUS
DOCUMENT NUMBER: 131:28684
TITLE: Natural protease inhibitors to hemorrhagins in snake venoms and their potential use in medicine
AUTHOR(S): Perez, John C.; Sanchez, Elda E.
CORPORATE SOURCE: Department of Biology, Texas A and M University-Kingsville, Kingsville, TX, 78363, USA
SOURCE: Toxicon (1999), 37(5), 703-728
CODEN: TOXIA6; ISSN: 0041-0101
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with many refs. Snake venoms are complex mixts. of many toxins and enzymes which effectively immobilize prey without a struggle and assist in digestion. Certain animals have a remarkable resistance to envenomation of snakes. Naturally occurring factors that neutralize snake venoms have been found in the sera of most snakes and a few warm-blooded animals. These antihemorrhagic and antineurotoxic factors have been purified from snake and mammalian sera. The antihemorrhagins are not Igs since they have different phys. and chem. characteristics. The natural immunity to hemorrhagins is the result of tissue inhibitors of metalloproteinases (TIMP) found in animal sera of resistant animals. Most animals have matrix metalloproteinases (MMP) and TIMP that are implicated in a wide variety of normal physiol. processes and pathol. conditions. MMP in animals have many biol. functions in embryogenesis, morphogenesis and tissue remodeling. MMP activities are precisely regulated by endogenous TIMP. Disruption of the balance between MMP and TIMP causes various diseases such as **arthritis**, periodontal diseases, diabetes, ophthalmol. conditions, neoplasia, metabolic bone disease, atherosclerosis and orthopedic conditions. Resistant animals that have a high titer of TIMP would have a survival advantage when bitten by poisonous snakes. Snake venoms are abundant and stable sources of MMP which are medically important. The venom MMP which cause unregulated destruction of tissue have sequences which have some degree of homol. with mammalian MMP which control normal biol. processes. Resistant animals are important sources of TIMP which can be used to study metalloproteinase related diseases. For these reasons the MMP in snakes and TIMP in resistant animal are excellent candidates for developing new drug therapies.

REFERENCE COUNT: 117 THERE ARE 117 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 29 OF 38 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1999:218785 HCAPLUS
DOCUMENT NUMBER: 130:290961
TITLE: Is there a role for antibiotics in the treatment of patients with **rheumatoid arthritis**?
AUTHOR(S): O'Dell, James R.
CORPORATE SOURCE: Department of Internal Medicine, Section of Rheumatology and Immunology, University of Nebraska Medical Center, Omaha, NE, USA
SOURCE: Drugs (1999), 57(3), 279-282
CODEN: DRUGAY; ISSN: 0012-6667
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with 38 refs. Despite many advances in the understanding and treatment of **rheumatoid arthritis**, its pathophysiol. remains incompletely understood. An infectious etiol. of **rheumatoid arthritis** has long been postulated but, even though many continue to believe that there is a "triggering agent for **rheumatoid arthritis**", none has been identified. Currently, both sulfasalazine and minocycline have been shown to be effective treatments for **rheumatoid arthritis** and are being used increasingly. In the case of minocycline, it appears that its ability to inhibit **metalloproteases** is an important characteristic that may account for some or part of its action against **rheumatoid arthritis**. Whether the antibacterial effects of these drugs or others are important in the treatment of **rheumatoid arthritis** continues to be investigated.
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 30 OF 38 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1998:648252 HCAPLUS
DOCUMENT NUMBER: 130:21979
TITLE: Matrix **metalloproteases**: variations on a theme
AUTHOR(S): Borkakoti, N.
CORPORATE SOURCE: Roche Discovery Welwyn, Welwyn Garden City, AL7 3AY, UK
SOURCE: Progress in Biophysics and Molecular Biology (1998), 70(1), 73-94
CODEN: PBIMAC; ISSN: 0079-6107
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with 76 refs. The family of proteins called matrix metalloproteinases (MMPs) are a class of structurally related proteins that are collectively responsible for the metab. of extracellular matrix proteins. These Zn- and Ca-dependent enzymes, which include the collagenases, stromelysins and gelatinases, are involved in normal tissue remodeling processes such as wound healing, pregnancy, and angiogenesis. Under physiol. conditions, in addn. to the regulated proteolysis of inactive precursors to the active form, the degradative nature of these enzymes are precisely controlled by endogenous inhibitors (TIMPs). The excess syntheses and prodn. of these proteins lead to the accelerated

matrix degrdn. assocd. with diseases such as **arthritis**, cancer, and multiple sclerosis. The MMPs have therefore proved to be attractive targets for structure-based drug design. The pursuit of low-mol.-wt. inhibitors of these proteins have encouraged structural studies on several members of family, so that the mol. details of enzyme-inhibitor interactions of the MMPs have become available. These studies provide insights into the basic structural framework of the MMP superfamily and reveal characteristics which promote specificity between individual members. The analyses of the 3-dimensional structure of the MMPs in the context of their primary sequence and the design and selectivity of low-mol.-wt. inhibitors of the superfamily is the subject of this review.

REFERENCE COUNT: 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 31 OF 38 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1998:637729 HCAPLUS
DOCUMENT NUMBER: 130:50944
TITLE: Interactions between T cell plasma membranes and monocytes
AUTHOR(S): Burger, Danielle; Dayer, Jean-Michel
CORPORATE SOURCE: Division of Immunology and Allergy, Hans Wilsdorf Laboratory, University Hospital, Geneva, CH-1211/14, Switz.
SOURCE: T Cells in Arthritis (1998), 111-128. Editor(s): Miossec, Pierre; Van den Berg, Wim B.; Firestein, Gary S. Birkhaeuser: Basel, Switz.
CODEN: 66SWA2
DOCUMENT TYPE: Conference; **General Review**
LANGUAGE: English

AB A review with 85 refs. Current data indicate that, by direct cell-to-cell contact, membranes of stimulated T cells attracted by specific chemokines, potentiate the inflammatory response. They do this by favoring the extravasation of cells from the immune system into the target tissue through the endothelium, and by activating the formation of pro-inflammatory cytokines and matrix **metalloproteases** (MMPs) at inflammatory sites, i.e., by stimulating monocytes and fibroblast-like cells. This mechanism induces an unbalanced prodn. of MMPs and TIMP-1 in vitro, and may, by analogy, favor tissue destruction in vivo. The authors thus hypothesize that cell-cell contact between stimulated T cells and surrounding cells represents an important mechanism contributing to the pathogenesis of inflammation and tissue destruction in chronic inflammatory diseases such as **rheumatoid arthritis**.

REFERENCE COUNT: 85 THERE ARE 85 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 32 OF 38 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1997:640889 HCAPLUS
DOCUMENT NUMBER: 127:276765
TITLE: Joint destruction and **rheumatoid arthritis**
AUTHOR(S): Asahara, Hiroshi; Nishioka, Kusuki
CORPORATE SOURCE: Nanbyo Chiryo Kenkyu Senta, Sei Marianna Ika Daigaku, Kawasaki, 216, Japan
SOURCE: Bone (Osaka) (1997), 11(3), 91-95
CODEN: BONEFN; ISSN: 0914-7047
PUBLISHER: Medikaru Rebyusha
DOCUMENT TYPE: Journal; **General Review**

LANGUAGE: Japanese

AB A review with 14 refs. Autoimmune nature of **rheumatoid arthritis** (RA) are discussed; penetration of memory type T cells and clonal proliferation of T cells in RA joints. Autoimmune process by generation of anti-matrix protein antibodies and mol. mimicry by virus infection are described for triggering RA. Synovial cell proliferation occurs in RA, and proteases play important roles in cartilage injury.

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ACCESSION NUMBER: 1997:474906 HCAPLUS
DOCUMENT NUMBER: 127:159695
TITLE: Upregulation of enzymic activity by interleukin-1 in osteoarthritis
AUTHOR(S): Chevalier, X.
CORPORATE SOURCE: Rheumatology Department, Hopital Henri-Mondor, boulevard de Lattre-de-Tassigny, Creteil, 94010, Fr.
SOURCE: Biomedicine & Pharmacotherapy (1997), 51(2), 58-62
CODEN: BIPHEX; ISSN: 0753-3322
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review, with 34 refs. Osteoarthritis is a slow progressive disease characterized by destruction of the articular cartilage. The degrdn. of extracellular matrix components is mainly mediated by a family of enzymes, the metalloproteinases (MMPs), which are active at neutral pH. Interleukin-1 (IL-1) is a small peptide, active in autocrine and paracrine fashions. In vitro IL-1 increases the prodn. of MMPs and inhibits the synthesis of collagen type II and proteoglycans. Its role in osteoarthritis is based on several findings: IL-1 is detectable in the synovial fluid and in the cartilage matrix of osteoarthritic joints; in vivo its deleterious actions can be reproduced by intra-articular injection of recombinant IL-1; biochem. changes obsd. in the cartilage matrix from osteoarthritic joints resemble those induced in vitro by IL-1; finally, antagonists of IL-1 are capable in vivo of preventing or at least diminishing the degrdn. of cartilage matrix components in several models of exptl. **arthritis**. Interleukin-1 appears to be a main factor mediating cartilage matrix destruction. However, its role in human osteoarthritis, although highly probable, remains to be detd.

L5 ANSWER 34 OF 38 HCAPLUS COPYRIGHT 2005 ACS on STN

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ACCESSION NUMBER: 1996:731566 HCAPLUS
DOCUMENT NUMBER: 126:102593
TITLE: Molecular mechanisms of joint destruction by the inflammatory factors such as protease, prostaglandin, hydrogen peroxide, and nitric oxide
AUTHOR(S): Sawai, Takashi; Nakamura, Hironori; Hashimoto, Michio; Tanaka, Maki
CORPORATE SOURCE: Hosp., Tohoku Univ., Sedai, 980-77, Japan
SOURCE: Saishin Igaku (1996), 51(12), 2344-2353
CODEN: SAIGAK; ISSN: 0370-8241
PUBLISHER: Saishin Igakusha
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: Japanese

AB A review with 22 refs., on formation and roles of proteases including matrix **metalloproteases**, prostaglandins, active oxygens, and NO in the pathogenesis of joint destruction in the **rheumatoid arthritis**.

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ACCESSION NUMBER: 1995:786874 HCAPLUS
DOCUMENT NUMBER: 123:191838
TITLE: Matrix **metalloproteases**: structure-based drug discovery targets
AUTHOR(S): Browner, Michelle F.
CORPORATE SOURCE: Mol. Structure Dept., Syntex Discovery Res., Alto, CA, 94303, USA
SOURCE: Perspectives in Drug Discovery and Design (1995), 2(3), 343-51
CODEN: PDDDEC; ISSN: 0928-2866
PUBLISHER: ESCOM
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review, with 44 refs. Matrix **metalloproteases** (MMPs) are a large family of mammalian zinc-dependent proteases that have garnered much attention as targets for drug discovery. In part, this interest is spurred by the central role these enzymes may play in diseases such as **arthritis** and cancer. One consequence of this attention has been the rapid accumulation of structure information. The structures of inhibitor-MMP complexes have provided a focus for drug discovery efforts in defining features of the MMP catalytic domain that will be crit. in developing potent and selective inhibitors. Inhibitor interactions at the active-size zinc are clearly important in defining the binding mode and relative inhibitor potency. Selective inhibitors will also, most likely, take advantage of the S1' substrate binding pocket, as there are relatively obvious differences at this site between the various members of the MMP family.

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ACCESSION NUMBER: 1992:487688 HCAPLUS
DOCUMENT NUMBER: 117:87688
TITLE: Role of neutral proteinases in rheumatoid joint destruction
AUTHOR(S): Okada, Yasunori
CORPORATE SOURCE: Sch. Allied Med. Prof., Kanazawa Univ., Kanazawa, 920, Japan
SOURCE: Igaku no Ayumi (1992), 161(9), 597-602
CODEN: IGAYAY; ISSN: 0039-2359
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: Japanese

AB A review with 22 refs. on the role of proteinases in arthropathy, matrix **metalloproteases**, serine proteases and their inhibitors, and reciprocal action of matrix **metalloproteases** and serine proteases.

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ACCESSION NUMBER: 1987:531760 HCAPLUS
DOCUMENT NUMBER: 107:131760
TITLE: Degradation of extracellular matrix in osteoarthritis: 4 fundamental questions
AUTHOR(S): Malemud, Charles J.; Martel-Pelletier, Johanne; Pelletier, Jean Pierre
CORPORATE SOURCE: Dep. Med., Case West. Reserve Univ., Cleveland, OH,

44106, USA
SOURCE: Journal of Rheumatology (1987), 14(Spec. Issue), 20-2
CODEN: JRHUA9; ISSN: 0315-162X
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with 31 refs. The destruction of articular cartilage is a hallmark of osteoarthritis. In this process, cartilage fibrillation and eventual erosive lesions result from altered biomechanics generally thought to be preceded by alterations in the cartilage extracellular matrix. The irreversible cartilage changes are, in part, mediated by elevated proteolytic activities of acid and neutral **metalloproteases** that degrade proteoglycan and Type II collagen. Interestingly, an identical enzyme class is believed to participate in normal turnover of thes extracellular matrix constituents. Thus, the control of synovial and cartilage protease activation has become of paramount importance in understanding the role these enzymes play in osteoarthritic pathol.

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ACCESSION NUMBER: 1978:457445 HCAPLUS
DOCUMENT NUMBER: 89:57445
TITLE: Enzymes in degenerative joint disease and antienzyme therapy
AUTHOR(S): Howell, David S.; Woessner, J. Frederick, Jr.; Sapolsky, Asher I.
CORPORATE SOURCE: Sch. Med., Univ. Miami, Miami, FL, USA
SOURCE: Hum. Jt. Health Dis. (1978), 128-31. Editor(s): Simon, William H. Univ. Pennsylvania Press: Philadelphia, Pa.
CODEN: 38INA8
DOCUMENT TYPE: Conference; **General Review**
LANGUAGE: English
AB A review with 18 refs. of the degrdn. of cartilage proteoglycan by cartilage neutral **metalloprotease** as a possible mechanism of cartilage degrdn. in osteoarthritis.

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